



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of : Confirmation No. 3969
Kazuhiko MATSUMURA et al. : Docket No. 2003_1003A
Serial No. 10/628,394 : Group Art Unit: 1626
Filed: July 29, 2003 : Examiner: Joseph K. McKane
METHOD FOR PRODUCING AN OPTICALLY ACTIVE β -AMINO ACID

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir,

I, Kazuhiko MATSUMURA, hereby declare that:

I was born in Osaka, Japan, in 1968.

I am an inventor of the above identified US patent Application.

I am a citizen of Japan and a resident of c/o Takasago International Corporation Central Research Laboratory, 4-11, Nishiyawata 1-chome, Hiratsuka-shi, Kanagawa 254-0073 JAPAN.

I am by profession a research chemist graduated the master of science from the Department of Chemistry, Faculty of Integrated Arts and Sciences, University of Osaka Prefecture in March 1992.

I have been employed from April 1992 by TAKASAGO INTERNATIONAL CORPORATION and have been engaged in the research work on stereo chemistry, production of various optically active products having asymmetric carbon atom or atoms, such as amino acids, alcohols, carboxylic acids and the like by the use of

catalysts, catalysts for asymmetric hydrogenating and various chemical science related to the stereo chemistry.

I was appointed as senior chemist in the year of 2005.

The following experiments have been carried out by myself or under my intimate supervision;

(1) Experiment part 1

Production of methyl (R)-3-aminobutanoate methanesulfonate

Under a nitrogen atmosphere, 78.0 mg (0.0869 mmol) of $\text{Ru}(\text{OCOCH}_3)_2((\text{R})\text{-tol-binap})$, 1.00g (8.69 mmol) of methyl 3-aminocrotonate, 0.83 g (8.69 mmol) of methanesulfonic acid and 5 ml of methanol were placed in a stainless steel autoclave, and the mixture was kept at 50 °C under 3MPa pressure of hydrogen for 15 hours with stirring. After completion of the reaction, the solvent was distilled off, and the residue was recrystallized from methanol/ethyl acetate to give the objective methyl (R)-3-aminobutanoate methanesulfonate (1.135 g, white crystals). The yield was 61.3%.

The enantiomeric excess was measured after conversion of the methyl (R)-3-aminobutanoate methanesulfonate obtained into methyl (R)-3-acetamidobutanoate by acetylation with acetic anhydride in the presence of triethylamine, and was found to be 85.0%ee.

$[\alpha]_D^{24} -9.3^\circ$ ($c=1.08$, CH_3OH); $^1\text{H-NMR}$ (CD_3OD): δ : 1.35 (d, $J=6.6\text{Hz}$), 2.70 (s, 3H), 2.69-2.72 (m, 2H), 3.64-3.72 (m, 1H), 3.74 (s, 3H); $^{13}\text{C-NMR}$ (CD_3OD): δ : 18.7, 38.8, 39.5, 45.7, 52.6, 172.2; EI-MS (m/z): 118 ($[\text{M}]^+$).

(2) Experiment part 2

Production of methyl (S)-3-aminobutanoate p-toluenesulfonate

Under a nitrogen atmosphere, 14.3 mg (0.00868 mmol) of $[\{\text{RuCl}((S)\text{-segphos})\}_2(\mu\text{-Cl})_3][\text{Me}_2\text{NH}_2]$, 1.00 g (3.48 mmol) of methyl 3-aminocrotonate p-toluenesulfonate 5 ml of methanol were placed in a stainless autoclave, and the mixture was kept at 50 °C under 3MPa pressure of hydrogen for 14 hours with stirring. After completion of the reaction, the solvent was distilled off, and the residue was recrystallized from methanol/methyl acetate to give the objective methyl (S)-3-aminobutanoate p-toluenesulfonate (0.473 g, white crystals). The yield was 47.0%.

The enantiomeric excess was determined after conversion into methyl(S)-3-acetamidobutanoate by acetylation with acetic anhydride to be 69.3%ee.

$^1\text{H-NMR}$ (DMSO-d_6): δ : 1.19 (d, $J = 6.6$ Hz, 3H), 2.28 (s, 3H), 2.50-2.70 (m, 2H), 3.40-3.60 (m, 1H), 3.63 (s, 3H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.70-8.00 (br, 3H).

(3) Experiment part 3

Production of methyl (-)-cis-2-aminocyclopentanecarboxylate methanesulfonate

Under a nitrogen atmosphere, 63.6 mg (0.0708 mmol) of $\text{Ru}(\text{OCOCH}_3)_2((R)\text{-tol-binap})$, 1.00g (7.08 mmol) of methyl 2-amino-1-cyclopentenecarboxylate, 0.68 g (7.084 mmol) of methanesulfonic acid and 5 ml of methanol were placed in a stainless steel autoclave, and the mixture was kept at 50 °C under 3MPa pressure of hydrogen for 15 hours with stirring. After completion of the reaction, the solvent was distilled off and the residue was recrystallized from methanol/ethyl acetate to give the objective methyl

(-)-cis-2-aminocyclopentanecarboxylate methanesulfonate
(0.643 g, white crystals). The yield was 37.9%.

$[\alpha]_D^{24}$ -27.5° (c=1.06, CH₃OH); ¹H-NMR (CD₃OD): δ: 1.66-1.80 (m, 2H), 1.81-1.91 (m, 2H), 2.70 (s, 3H), 2.84-2.92 (m, 1H), 3.74 (s, 3H), 3.83 (br q, J=ca.7.5Hz); ¹³C-NMR (CD₃OD): δ: 24.1, 30.0, 31.9, 39.5, 49.6, 52.8, 55.3, 174.8; EI-MS (m/z): 143 ([M]⁺).

(4) Experiment part 4

Under a nitrogen atmosphere, 195.0 mg (0.217 mmol) of Ru(OAc)₂((R)-tol-binap), 5.00 g (43.43 mmol) of methyl 3-aminocrotonate, 2.61 g (43.43 mmol) of acetic acid, 4.35 g (43.43 mmol) of 2,2,2-trifluoroethanol and 25 ml of methanol were placed in a stainless steel autoclave, and the mixture was kept at 80 °C under 3 MPa pressure of hydrogen for 15 hours with stirring. After completion of the reaction, the solvent was removed by evaporation to give methyl (3R)-3-aminobutanoate acetate as a crude material (8.97 g). The enantiomeric excess of methyl (3R)-3-aminobutanoate in the crude product was determined to be 82.9% ee by HPLC analysis using a CHIRALCEL OD-H column (4.6 x 250 mm, available from DAICEL CHEMICAL INDUSTRIES, LTD.) after conversion into methyl (3R)-3-(4-nitrobenzoylamino)butanoate.

The resulting crude material (8.97 g) was dissolved in methyl acetate (60 mL), and to the solution was added dropwise a solution of p-toluenesulfonic acid monohydrate (8.26 g, 43.43 mmol) in methyl acetate (60 mL) at 50 °C over a period of 30 minutes. The mixture was stirred at room temperature for 1 hour and cooled down to 0 °C to precipitate a solid. The solid was collected by filtration to give methyl (3R)-3-aminobutanoate

p-toluenesulfonate (7.90 g, white crystal) in 62.9% yield. The enantiomeric excess of the product obtained above was determined to be 92.1% ee after conversion into methyl (3R)-3-(4-nitrobenzoylamino)butanoate in a similar manner to the crude product.

I declare also that a silica gel chromatography mentioned in the United States Patent Application No. 10/628,394 filed on July 29, 2003 does not work for the resolution of racemate.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 18 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

June 23, 2005

Dated

Kazuhiko Matsumura

Kazuhiko MATSUMURA